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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/816,099 | 03/31/2004 | Katalin Varadi | P-279.00 | 9454 |

7590 08/01/2005

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| EXAMINER | |
|---|---|
| KOSSON, ROSANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | |

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/816,099 | VARADI ET AL. | |
| | Examiner | Art Unit | |
| | Rosanne Kosson | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *14-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



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## DETAILED ACTION

### *Election/Restrictions*

Applicants' election without traverse of Group I, claims 1-13, 22 and 23, in the reply filed on June 30, 2005 is acknowledged. Claims 14-21 are withdrawn from prosecution as being drawn to non-elected inventions.

No claims have been amended, added or canceled. Accordingly, claims 1-13, 22 and 23 are examined on the merits herewith.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et a. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019).

Wöber et al. disclose reagents and an assay for measuring thrombin generation. They disclose natural tissue factor (TF) as a dry powder and solutions of the phospholipids phosphatidylserine (PS) and phosphatidylcholine (PC). Wöber et al. also disclose that these three reagents are combined to prepare a solution of vesicles or liposomes containing TF, i.e., a TF/PL complex. The ratio of PC to PS in this complex is 6:4. This solution may be frozen in assay portions (see col. 3, lines 9-16, and col. 4, lines 13-46). Wöber et al. also disclose a thrombin standard that is used in their assay (see col. 5, lines 20-40). Wöber et al. do not disclose that this complex is lyophilized or the concentrations of TF and PL in the complex.

Hawkins et al., however, disclose that the TF/PL solution may be lyophilized. The ratio of PC to PS in Hawkins et al. is 7:3 (see Example 2 in col. 8 and Example 4 in cols. 9 and 10). The ratio of TF to PL is 1:2000 to 1:20,000, and the PL concentration is 1-300 μM (see col. 4, lines 34-50). At a PL concentration of 1 μM, the TF concentration is 50-500 pM. Synthetic (recombinant) or natural TF may be used, and synthetic or

natural phospholipids may be used. Combinations of lipids other than PC and PC may be used (see col. 4, lines 34-62, and col. 5, lines 3-10).

One of ordinary skill in the art at the time that invention was made would have been motivated to lyophilize the TF/PL preparation, because Hawkins et al. teach that this preparation is made as a reagent for performing assays to measure prothrombin time (see Title). This reagent is meant to be used for large-scale clinical assays and is designed to have minimal variability from lot to lot (see col. 1, line 36, to col. 2, line 7. One of ordinary skill in the art would have recognized that a manufacturer of such a reagent would have lyophilized it to reduce the weight and volume for shipping purposes and to impart stability to the reagent. Dry materials are less susceptible to degradation than their liquid form, e.g., as with powdered vs. liquid milk.

One of ordinary skill in the art would have been motivated to prepare a TF/PL complex with the TF and PL concentrations and with the phospholipid ratios disclosed in Hawkins et al., because Hawkins et al. teach that these are suitable amounts for preparing a reagent for an assay for measuring prothrombin time. Prothrombin is a thrombin precursor in the clotting pathway (cleaved by the protease prothrombinase to form thrombin). Thus a reagent for measuring prothrombin time may also be used to measure thrombin time.

Regarding the lyophilized thrombin substrate and $CaCl_2$ preparation, Wöber et al. disclose a dry chromogenic thrombin substrate, S 2238 (Chromogenix, now Diapharma) that is soluble in water and that the thrombin reaction is initiated by the addition of $CaCl_2$ to the assay samples (see col. 5, lines 10-25). One of ordinary skill in the art would

have been motivated to prepare a lyophilized reagent containing thrombin substrate and $CaCl_2$, because Hawkins et al. teach the advantages of lyophilized reagents in clinical assays. As noted above, the artisan of ordinary skill would have recognized that aqueous solutions can be lyophilized to reduce bulk and improve stability. One of ordinary skill in the art would also have recognized that the thrombin substrate and $CaCl_2$ are both soluble in water or buffer, as disclosed by Wöber et al., and they would have been combined because an enzymatic reaction may also be initiated by the addition of substrate, as well as by the addition of a catalytic substance or cofactor. In an assay of a number of samples, the enzymatic reaction is initiated by the addition of a reagent, ideally simultaneously to all samples, but this reagent may contain the substrate and the cofactor. Combining the substrate and the cofactor reduces the number of pipetting steps, thereby reducing the chance of assay errors due to pipetting errors, and reduces the number of assay steps, allowing the assay to be performed faster. Because the thrombin substrate and $CaCl_2$ are both soluble in water or buffer, one of ordinary skill in the art would have recognized that a solution containing both of these substances would have been prepared and lyophilized. Moreover, Hogan et al. teach that, in a diagnostic kit, or when performing an assay with a diagnostic kit, the reagents may be premixed before lyophilization so that, when reconstituted, a complete mixture is formed with the reagents in the proper ratio and ready for use (see col. 37, lines 14-29).

Regarding a thrombin substrate containing a fluorescent label, as noted above, Wöber et al. disclose a substrate containing a colored label. Determinations of thrombin

generation are made by measuring the extinction over five minutes at one minute intervals at 405 nm (see col. 5, lines 33-40). Váradi et al., however, disclose a thrombin substrate for a thrombin generation assay that contains a fluorescent label, Z-Gly-Gly-Arg-AMC. In the assay samples, increases in fluorescence were measured every minute over 2 hours at 460 nm (see p. 2375, Thrombin generation assay). Lawson et al. also disclose a thrombin substrate for a thrombin generation assay that contains a fluorescent label, m-LGR-nds. In the assay samples, increases in fluorescence were measured frequently over 60 minutes (see p. 4837, Results, and p. 4836, left col., last full paragraph). One of ordinary skill in the art would have been motivated to use the thrombin substrate of Váradi et al. or Lawson et al. as the thrombin substrate in the set of reagents disclosed by Wöber et al., i.e., a fluorescent label instead of a colored label, because Váradi et al. and Lawson et al. teach that their substrates are available as dry powders that are soluble in the buffers used in a thrombin generation assay. Thus, lyophilized forms of these powders may also be prepared. One of ordinary skill in the art would have recognized that these substrates are interchangeable with the substrate of Wöber et al., as it would have been well within his capability, when performing a thrombin generation assay, to measure the amount of fluorescence produced over time by a thrombin reaction product instead of the amount of color generated over time by a thrombin reaction product. Both fluorometric and spectrophotometric measurements are standard assay techniques.

With respect to claim 8, which recites phospholipids comprising PC, PS and PE (polyethanolamine) in a ratio of about 60:20:20 to about 78:17:5, the composition of

phospholipid mixtures and the ratios of the different lipid components are result-effective parameters which were routinely optimized by one of ordinary skill in the art. Thus, the claimed variations in Applicants' composition with respect to these parameters clearly would have been obvious at the time of Applicants' invention, the optimization of these parameters being well within the capabilities of the artisan of ordinary skill at the time of Applicants' invention. Additionally, liposomes comprising such a lipid mixture were known at the time of Applicants' invention. Chan (US 5,952,198) discloses liposomes of PC, PS, and PE in a ratio of 4:1:1 that are added to the medium of 293S cells (human embryonic kidney cells) to increase the production of recombinant Factor VIII, a clotting factor. Liposomes of PC, PS and PE in a ratio of 8:1:1 and 16:2:1 are also disclosed (see Table 1, cols. 3 and 4). It is thought that these liposomes stabilize the recombinant Factor VIII in an in vitro medium (see col. 1, lines 49-52). The liposomes with a ratio of 4:1:1 and 16:2:1 are close to those in Applicants' claimed range. One of ordinary skill in the art would have been motivated to use liposomes comprising PC, PS and PE in a ratio of about 60:20:20 to about 78:17:5 instead of liposomes comprising PC and PS in a ratio of 6:4 in a complex with TF because Chen teaches that the PC:PS:PE liposomes have a stabilizing effect on clotting factors, Factor VIII and von Willebrand factor. As noted above, Hawkins discloses that lipid mixtures other than PC:PS, 6:4, may be used in the TF/PL complex.

Regarding a solid support, such as microtiter plate, with lyophilized assay reagents coated onto the wells or assay vessels of the support, and a method of performing an assay using this solid support, Weinstein et al. disclose an assay method

using a solid support such as a microtiter plate in which lyophilized detection reagents are immobilized on the solid support (see col. 16, lines 10-25, and col. 17, lines 5-6). The advantages of performing an assay with this solid support are that the assay is fast and simple and designed for screening a large number of samples (see col. 17, lines 22-30). Dubrow et al. also disclose performing an assay with minute amounts of lyophilized reagents immobilized on a solid support (see col. 12, line 59, to col. 13, line 11). Current trends in biochemical analyses have been toward miniaturization, particularly in microfluidics systems (which manipulate microtiter plates), and which have the advantages of small amounts of reagents needed, faster throughput, automation and improved data (see col. 1, lines 12-19). One of ordinary skill in the art would have been motivated to prepare a kit for measuring thrombin generation comprising assay reagents lyophilized and immobilized on a solid support, because Hawkins et al. teach the advantages of lyophilized reagents, and Weinstein et al. and Dubrow et al. teach the advantages of formulating these reagents as a lyophilized coating on a solid support. Weinstein et al., more specifically, teach the advantages of formulating assay reagents as a lyophilized coating on the wells of a microtiter plate. The cited references also teach the benefits of performing assays with these solid supports (speed, simplicity, high throughput, improved data).

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1653

rk/2005-07-14

ROBERT A. WAX
PRIMARY EXAMINER